00005.001278 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	:	Examiner: Melenie Lee McCormick
TOSHIKAZU KAMIYA, ET AL.	)	
	:	Group Art Unit: 1655
Application No.: 10/552,526	)	
	:	Conformation No. 4344
Filed: October 11, 2005	)	
	:	
For: ARTHRITIS PREVENTING OR TREATING AGENT	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 C. F. R. 1.132

Sir:

I, Toshikazu Kamiya, of 360-17, Hitachino-higashi, Ushiku-shi, Ibaraki 300-1207, Japan do hereby declare as follows:

1. I received a Bachelors of Science degree from the Department of Agriculture of Tokyo University in March, 1982. I was awarded a Ph.D. degree in Agricultural Chemistry from Tokyo University in 1988.

2. Since April, 1984, I have been employed by Kyowa Hakko Kogyo Co., Ltd., whose name was changed to Kyowa Hakko Bio Co. Ltd., (both referred to collectively herein as "Kyowa Hakko") after its merger with Kirin Holdings Co., Ltd., in October, 2008.

3. I was assigned to Tokyo Research Laboratories of Kyowa Hakko in July 1987, and was engaged in the research and development of pharmaceutical products. From October 1994 through March 1996, I conducted eye-disease related research at the National Eye Institute, National Institutes of Health in the United States, while maintaining my title and position at Kyowa Hakko. From March 1997 through March 2004, I was engaged as a Senior Scientist in research and development of nutraceutical products at the Tsukuba Research Laboratories of Kyowa Hakko. From April 2004 through July 2009, I played a role as Director of Kyowa Hakko, being engaged in managing all research activities of the Healthcare Research Laboratories (which in 2008 was renamed Healthcare Products Development Center). Since August 1st, 2009, I have been General Manager, Healthcare, of Fine Chemicals Department, Kyowa Hakko Bio Co., Ltd.

4. I am one of the co-inventors of the invention described and claimed in the application and have a full knowledge of the present invention, the cited references and the Examiner's rejection of the pending claims thereover. Having a doctorate degree in Agricultural Chemistry and having conducted more than twenty years in designing pharmaceuticals and nutraceuticals, I am one of ordinary skill in this art.

5. I am aware that in the April 1, 2009 Office Action, at page 12, the Examiner states:

> *"Applicants also argue that the present invention achieves unexpectedly superior results over the closest prior art and point to example 3 at pages 38-40 of the specification. This is not found persuasive. The decrease in the arthritic score for the claimed composition (group 4) is not greater than the additive effects of groups 2 and 3. As compared to group 1, group 2 results in 1.74 point decrease. As compared to group 1, group 3 results in a 1.0 point decrease. Using both compositions together at least a 2.74 decrease would be*

expected. Group 4 results in a 2.74 point decrease. Therefore, the results are not unexpected."

6. For completeness, I am excerpting the following experiments which appear as "Example 3" in the specification of the present application to explain what such teaches to one of ordinary skill in this art.

7. Example 3 evaluates the suppressive effect on arthritis using the art-accepted model of administering collagen to induce arthritis in mice [*Nature*, Vol. 283 (1980) 666-68]. As the first administration of collagen, 100 μl/mouse of an emulsified 50/50 mixture of type-2 collagen and Freund's complete adjuvant was intracutaneously administered to the root of a male DBA/1J mouse of 6 weeks age. At day 21 after the first administration of collagen, 100 μl/mouse of an emulsified 50/50 mixture of type-2 collagen and Freund's complete adjuvant was similarly intracutaneously administered to the root of the tail as the 2nd administration.

From the first day of administration of collagen, (i) commercially available powder feed CE-2 was ingested by mice of group 1, (ii) CE-2 with 0.5% by weight of amacha extract (prepared according to Example 2) was ingested by mice of group 2, (iii) CE-2 with 1.0% by weight of D-glucosamine sulfate disodium chloride and 1.0% by weight of sodium chondroitin sulfate was ingested by mice of group 3 and (iv) CE-2 with 0.25% by weight of amacha extract, 0.5% by weight of D-glucosamine sulfate disodium chloride and 0.5% by weight of chondroitin sulfate was ingested by mice of group 4. CE-2 was also ingested by an untreated group to which no type-2 collagen was administered.

On the 27th, 30th and 34th days after the first administration of type-2 collagen, degree of onset of arthritis was scored by applying 0-4 points with respect to

each paw of the mouse as follows: 0 point for no symptoms, 1 point for light swelling on one finger (or ankle), 2 points for swelling on 1 to 3 fingers (or ankle), 3 points for swelling on 3 to 5 fingers and ankle, and 4 points for swelling on all fingers and ankle. The total score of 4 paws of the mouse (e.g., points 0 to 16) was then recorded and presented in terms of mean value ± standard error (n = 20).

Additive(s)		Scores for Arthritis			
		0 day	27 days	30 days	34 days
Untreated Gr	—	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Group 1	—	0.00 ± 0.00	6.65 ± 0.48	11.70 ± 0.56	13.30 ± 0.59
Group 2	Amacha extract (0.5%)	0.00 ± 0.00	5.44 ± 0.51	10.11 ± 0.75	11.56 ± 0.72
Group 3	Glucosamine (1.0%) and Chondroitin Sulfate (1.0%)	0.00 ± 0.00	5.60 ± 0.41	10.65 ± 0.64	12.30 ± 0.60
Group 4	Amacha extract (0.25%), Glucosamine (0.5%) and Chondroitin Sulfate (0.5%)	0.00 ± 0.00	4.00 ± 0.68	8.29 ± 1.11	10.56 ± 1.04

8. Although the Examiner correctly states that

> "As compared to group 1, group 2 results in 1.74 point decrease. As compared to group 1, group 3 results in a 1.0 point decrease. Group 4 results in a 2.74 point decrease",

the results of group 2 and group 3 show that the power of 0.5% amacha extract is 1.74 point and that of the mixture of 1.0% glucosamine and 1.0% chondroitin sulfate is 1.0 points. If Applicants had used the mixture of all three components at the same concentrations as used in group 2 and group 3, the mixture would be expected to have the power of 2.74 points as asserted by the Examiner.

9. However, in group 4, Applicants reduced by half the amounts of amacha extract, glucosamine, and chondroitin sulfate, to half of those used in groups 2 and 3, namely, from 0.5% to 0.25%, from 1% to 0.5%, and from 1% to 0.5%, respectively.

10. If amacha extract, glucosamine, and chondroitin sulfate had merely an additional effect, the power of the mixture of all these at the concentrations used in the group 4 would have been the sum of 1.74/2 plus 1.0/2 (e.g., 0.87 and 0.5, respectively, for a total of 1.37 points). Instead, the efficacy observed in the group 4 was 2.74 points, far greater than the Examiner's expected 1.37 points.

11. These results show that the effect in Group 4 is far higher than the effect presumed from the results of Groups 2 and 3 and that, when glucosamine and chondroitin sulfate are combined with amacha extract, progress of arthritis can be synergistically suppressed.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Toshikazu Kamiya

Date: Aug 7, 2009

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